10/566,252

STN FILE CAPLUS 3/8/07

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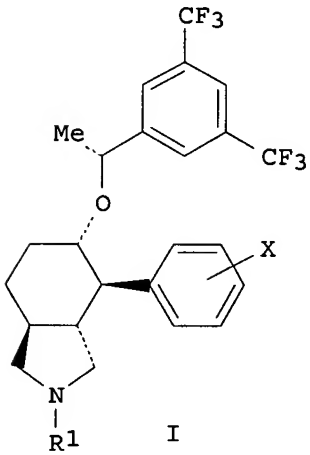
L5 ANSWER 1 OF 37 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:63559 CAPLUS
DOCUMENT NUMBER: 146:163006
TITLE: Process for making hydroisoindoline tachykinin receptor antagonists
INVENTOR(S): Kuethe, Jeffrey T.; Yin, Jingjun; Huffman, Mark A.; Journet, Michel
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 52pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2007008564	A1	20070118	WO 2006-US26293		20060707
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW					
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
US 2007015923	A1	20070118	US 2006-484208		20060711
PRIORITY APPLN. INFO.:			US 2005-698237P	P	20050711
			US 2005-698761P	P	20050713

OTHER SOURCE(S): CASREACT 146:163006
GI



I

AB The invention is directed to a process for preparing hydroisoindoline compds. I [R1 is H, alkyl which may be substituted by halogen, hydroxyl or Ph, cyclopentenone which may be substituted by halogen, hydroxyl or Me, alkanoyl, H2NCO, or alkylcarbamoyl; X is H, F, or Me] or pharmaceutically-acceptable salts, which are useful as neurokinin-1 (

AB 3-Substituted quinoline-4-carboxamide derivs. [I; wherein R1 = H, alkyl; R2 = aryl, cycloalkyl, heteroaryl; R3 = H, alkyl, wherein the alkyl group may be optionally substituted by one or more fluorine atoms; R4 = H, hydroxyalkyl, dihydroxyalkyl, hydroxyalkoxyalkyl; R5 = branched or linear alkyl, cycloalkyl, cycloalkylalkyl, aryl, single or fused ring aromatic heterocyclic group; R6 = H, alkyl, alkenyl, aryl, alkoxy, hydroxy, halo, nitro, cyano, carboxy, carboxamido, sulfonamido, trifluoromethyl, amino, mono- or di-alkylamino; R7 = H, halo; R8 = H, O] were prepared For example, 3-[4-(2-hydroxyethyl)-3-oxopiperazin-1-ylmethyl]-2-thiophen-2-ylquinoline-4-carboxylic acid ((S)-1-cyclohexylethyl)amide was prepared by a multistep procedure. The prepared compds. were useful as nk-2 and nk-3 receptor antagonists.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 16 OF 37 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:679720 CAPLUS
DOCUMENT NUMBER: 138:378998
TITLE: Tonic immobility in guinea pigs: A behavioural response for detecting an anxiolytic-like effect?
AUTHOR(S): Olsen, C. K.; Hogg, S.; Lapiz, M. D. S.
CORPORATE SOURCE: Pharmacol. Res., H. Lundbeck A/S, Copenhagen, DK-2500, Den.
SOURCE: Behavioural Pharmacology (2002), 13(4), 261-269
CODEN: BPHAEL; ISSN: 0955-8810
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tonic immobility (TI) is considered to be an innate fear response characterized by a temporary state of profound and reversible motor inhibition. TI occurs in a wide range of species in a predator-prey confrontation and is hypothesized to be a terminal defense response occurring when there is phys. contact between prey and predator. The objective of the present study was to investigate the validity of the TI model in guinea pigs for detection of anxiolytic and/or antidepressant drug activity. Compds. that reduced TI include the serotonin (5-HT) releaser fenfluramine, the 5-HT1A receptor agonists 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) and buspirone, the 5-HT2C/2B receptor antagonist SB 206553, the 5-HT2A receptor antagonist MDL 100151, but only at doses thought also to inhibit 5-HT2C receptors, the noradrenaline (NA) reuptake inhibitor desipramine, the benzodiazepine inverse agonist FG-7142, the α2-adrenergic receptor antagonist yohimbine, the neurokinin (NK)1 receptor antagonist L-733060, and the NK2 receptor antagonist SR-48968. Compds. that increased TI include the benzodiazepine agonists diazepam and alprazolam, and the α2-adrenergic receptor agonist clonidine. The selective 5-HT reuptake inhibitors citalopram, paroxetine and fluoxetine, the 5-HT1A receptor antagonist WAY 100635, the 5-HT2C receptor agonist MK-212, the 5-HT/NA reuptake inhibitor imipramine, the NA reuptake inhibitor talopram, the benzodiazepine antagonist flumazenil, the α2-adrenergic receptor antagonist idazoxan and the psychostimulant amphetamine did not have any effect. These findings indicate that the serotonergic, noradrenergic and neurokinin systems are involved in mediating or modulating TI behavior in guinea pigs. The potential of TI as a behavior for detecting anxiolytic-like effect may be questioned due to the contradictory effect of the benzodiazepine ligands, which may be attributed to the sedative and/or ataxic effects of the compds. Nevertheless, there is preclin. evidence suggesting that 5-HT1A receptor agonists, 5-HT2C receptor antagonists and NK1 and NK2 receptor antagonists possess anxiolytic potential. Only when results of clin. investigations of the anxiolytic potential of non-benzodiazepine ligands (for example the NK receptor antagonists) are available, will it be possible to determine fully the

HR 2001000862	A1	20030630	HR 2001-862		20011120
ZA 2001009555	A	20040407	ZA 2001-9555		20011120
BG 106208	A	20020930	BG 2001-106208		20011211
PRIORITY APPLN. INFO.:			US 1999-135520P	P	19990521
			WO 2000-IB295	W	20000316

AB New pharmaceutical uses are provided for compds. that exhibit activity as NOS inhibitors. Specifically, the invention provides the use of NOS inhibitors, particularly selective neuronal NOS (nNOS) inhibitors, alone or in combination with another active agent, in particular, either a selective serotonin reuptake inhibitor (SSRI) or an NK-1 receptor antagonist, for the treatment of disorders or conditions the treatment which can be effected or facilitated by altering circadian rhythms. Examples of such disorders and conditions are blindness, obesity, seasonal affective disorder, bipolar disorder, jet lag, circadian sleep rhythms disorder, sleep deprivation, parasomnias, REM sleep disorders, hypersomnia, sleep-wake cycle disorders, narcolepsy and sleep disorders associated with shift work or irregular work schedules; nocturnal enuresis, and restless-legs syndrome.

L5 ANSWER 26 OF 37 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	2000:834889 CAPLUS
DOCUMENT NUMBER:	134:247147
TITLE:	NKP608: a selective NK-1 receptor antagonist with anxiolytic-like effects in the social interaction and social exploration test in rats
AUTHOR(S):	Vassout, A.; Veenstra, S.; Hauser, K.; Ofner, S.; Brugger, F.; Schilling, W.; Gentsch, C.
CORPORATE SOURCE:	Nervous System, Research, Pharma Novartis AG, Basel, CH-4002, Switz.
SOURCE:	Regulatory Peptides (2000), 96(1-2), 7-16 CODEN: REPPDY; ISSN: 0167-0115
PUBLISHER:	Elsevier Science Ireland Ltd.
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB NKP608 is a non-peptidic derivative of 4-aminopiperidine which acts as a selective, specific and potent antagonist at the neurokinin-1 (NK-1) receptor both in vitro and in vivo. In vitro, the binding of NKP608 to bovine retina was characterized by an IC50 of 2.6±0.4 nM, whereas the compound affinity to other receptor binding sites, including NK-2 and NK-3, was much lower. Species differences in IC50 values with NKP608 were less pronounced than with previously described NK-1 receptor antagonists, being 13±2 and 27±2 nM in gerbil midbrain and rat striatum, resp. In vivo, using the hind foot thumping model in gerbils, NKP608 exhibited a potent NK-1 antagonistic activity following oral administration (ID50=0.23 mg/kg; 2 h pretreatment), supporting a central activity of NKP608. The compound had a long duration of action with an ID50 value of 0.15 mg/kg p.o. and 0.38 mg/kg p.o. following a pretreatment of 5 and 24 h, resp. Following a subchronic administration for 7 consecutive days (once daily) there was no evidence for the development of tolerance or accumulation. In the social interaction test performed in a highly illuminated, unfamiliar test arena, NKP608 specifically increased the time the two rats spent in social contact, and there was no concomitant increase in parameters reflecting general activity, i.e. ambulation (number of square entries) or the number of rearings. Active social time was maximally increased at a dose range of 0.01-1 mg/kg p.o. NKP608, the effect being weaker or absent at both lower (0.001 mg/kg p.o.) and higher (10 mg/kg p.o.) doses. A comparable bell-shaped dose-response relation was seen in the social exploration test in rats. In this modified resident/intruder paradigm, maximal increase in social contact of the intruder rat directed towards the resident rat was seen at a similar dose range (0.03-3 mg/kg p.o.). tests. The effects observed following an acute oral administration of NKP608 were comparable to

those seen following a treatment with the well-known benzodiazepine, chlordiazepoxide. These findings indicate that the drug exhibits an anxiolytic-like effect and that this effect, as concluded from the observed antagonism of the hind foot thumping induced by i.c.v. administration of the NK-1 receptor agonist SPOMe, is centrally mediated. This makes this compound a potentially promising candidate for treating anxiety -related disorders in humans.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 27 OF 37 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:828309 CAPLUS
DOCUMENT NUMBER: 134:37123
TITLE: The psychopharmacology of tachykinin NK-3 receptors in laboratory animals
AUTHOR(S): Massi, M.; Panocka, I.; de Caro, G.
CORPORATE SOURCE: Department of Pharmacological Sciences and Experimental Medicine, University of Camerino, Camerino, 62032, Italy
SOURCE: Peptides (New York) (2000), 21(11), 1597-1609
CODEN: PPTDD5; ISSN: 0196-9781
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 149 refs. The present article reviews the studies so far published on the psychopharmacol. effects mediated by tachykinin NK-3 receptors in laboratory animals. Central administration of NK-3 receptor agonists has been reported to attenuate alc. intake in alc.-preferring rats and to evoke conditioned place preference. These findings suggest that NK-3 receptors may affect reward processes to drugs of abuse. Anxiolytic-like and antidepressant-like effects have been previously reported for NK-1 receptor antagonists, and anxiolytic-like effects for NK-2 receptor antagonists. More recently, it has been shown that NK-3 receptor agonists have anxiolytic-like and antidepressant-like effects in mice and rats, while an NK-3 receptor antagonist was reported to be anxiogenic in mice. These findings indicate that different tachykinin receptor subtypes may be involved in anxiolytic-like and antidepressant-like effects in laboratory animals and raise interest for the possible role of NK-3 receptors in the control of anxiety and depression in man.
REFERENCE COUNT: 149 THERE ARE 149 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 28 OF 37 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:785161 CAPLUS
DOCUMENT NUMBER: 134:94
TITLE: Update on substance P (NK - 1 receptor) antagonists in clinical trials for depression
AUTHOR(S): Kramer, M. S.
CORPORATE SOURCE: Merck Research Laboratories, Merck and Co., West Point, PA, 19422, USA
SOURCE: Neuropeptides (Edinburgh) (2000), 34(5), 255
CODEN: NRPPDD; ISSN: 0143-4179
PUBLISHER: Harcourt Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 4 refs. In 1998 we reported in Science that a selective SP (NK1 receptor) antagonist was an effective and well-tolerated antidepressant in a placebo and active controlled (paroxetine) study of 210 patients with major depression. This finding encouraged our laboratory to

conduct a very large dose finding study of the same compound in patients with major depression, and to continue research on the effects of NK1 antagonism in preclin. paradigms related to affective/anxiety disorders. In view of the inherent difficulty in obtaining informative antidepressant studies, we set out to design the subsequent series of studies with the second compound with ever more rigor. The current round of clin. studies is projected to be completed sometime in the first part of 2001.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 29 OF 37 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:688232 CAPLUS
DOCUMENT NUMBER: 133:266729
TITLE: Preparation of novel substituted tetrahydropyrans as neurokinin 1 (NK-1) receptor antagonists
INVENTOR(S): Owen, Simon Neil; Seward, Eileen Mary; Swain, Christopher John; Williams, Brian John
PATENT ASSIGNEE(S): Merck Sharp & Dohme Limited, UK
SOURCE: PCT Int. Appl., 149 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2000056727	A1	20000928	WO 2000-GB974		20000316
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2367985	A1	20000928	CA 2000-2367985		20000316
EP 1165540	A1	20020102	EP 2000-911045		20000316
EP 1165540	B1	20030813			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
AU 746251	B2	20020418	AU 2000-33042		20000316
HU 200200441	A2	20020729	HU 2002-441		20000316
JP 2002540107	T	20021126	JP 2000-606588		20000316
AT 247096	T	20030815	AT 2000-911045		20000316
ES 2203434	T3	20040416	ES 2000-911045		20000316
ZA 2001006844	A	20020820	ZA 2001-6844		20010820
IN 2001CN01225	A	20050304	IN 2001-CN1225		20010903
US 6458830	B1	20021001	US 2001-936343		20010910
PRIORITY APPLN. INFO.:			GB 1999-6480	A	19990319
			GB 1999-24616	A	19991018
			WO 2000-GB974	W	20000316

OTHER SOURCE(S): MARPAT 133:266729
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Substituted tetrahydropyrans I [R1, R4 = H, halo, alkyl, alkoxy,

fluoroalkyl, fluoroalkoxy, cycloalkyl(alkyl), NO2, CN, SRa, SORa, SO2Ra, CO2Ra, CONRaRb (Ra or Rb = H, alkyl), alkenyl, alkynyl, alkoxy(alkyl); R2, R5 = H, halo, alkyl, fluoroalkyl, alkoxyalkoxy; R3 = H, halo, fluoroalkyl; R6 = H, alkyl, hydroxyalkyl; R7 = halo, hydroxy, (un)substituted alkenyl, (un)substituted alkynyl, N3, -NR11R12, -NRaCORb, -OSO2Ra, -(CH2)pNRa(CH2)qCOORb (p or q = 1, 2), CORa, COORa, -N=C=O, or N/O/S heterocycle bound at N optionally substituted by oxo, thioxo, halogen, hydroxy, thiol, CORa, CO2Ra, -ZNR11R12 (Z = bond, cyclo(alkylene)), alkyl, hydroxyalkyl, haloalkyl, alkoxy, fluoroalkoxy or alkoxy substituted by a alkoxy or hydroxyl group (R11 = H, alkyl, cycloalkyl, cycloalkylalkyl, alkyl substituted by alkoxy or hydroxyl group, five or six membered N heterocycle; R12 = H, alkyl, cycloalkyl, cycloalkylalkyl, alkyl substituted by alkoxy or hydroxyl group); R8 = hydrogen, alkyl, fluoroalkyl, hydroxy, alkoxy, hydroxyalkyl; R9 or R10 = H, halo, alkyl, oxo, CO2Ra, CONRaRb, CH2ORc (Rc = H, alkyl, phenyl); n = 0, 1 or 2] and pharmaceutically acceptable salts thereof were prepared as neurokinin 1 (NK-1) receptor antagonists. Thus, tetrahydropyran II (R = Me2N) was prepared via nucleophilic substitution of the corresponding mesylate II (R = MeSO2O). The compds. are of particular use in the treatment or prevention of depression, anxiety, pain, inflammation, migraine, emesis or postherpetic neuralgia (no data).

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 30 OF 37 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:636208 CAPLUS
DOCUMENT NUMBER: 133:217713
TITLE: Use of a NK-1 receptor antagonist and an antidepressant and/or an anti-anxiety agent for the treatment or prevention of depression and/or anxiety
INVENTOR(S): Carlson, Emma Joanne; Rupniak, Nadia Melanie
PATENT ASSIGNEE(S): Merck Sharp and Dohme Ltd., UK
SOURCE: U.S., 28 pp., Cont.-in-part of WO1997GB 9702748.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6117855	A	20000912	US 1997-994063	19971219
WO 9815277	A2	19980416	WO 1997-GB2748	19971007
WO 9815277	A3	19980522		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 6319953	B1	20011120	US 1999-457241	19991208
US 2002042361	A1	20020411	US 2001-978437	20011016
US 6649614	B2	20031118		

PRIORITY APPLN. INFO.:

GB 1996-20880	A	19961007
GB 1997-16458	A	19970804
GB 1997-16460	A	19970804
WO 1997-GB2748	A2	19971007
US 1997-994063	A3	19971219
US 1999-457241	A3	19991208

OTHER SOURCE(S): MARPAT 133:217713

CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-632861P P 20041203

OTHER SOURCE(S): MARPAT 145:27877

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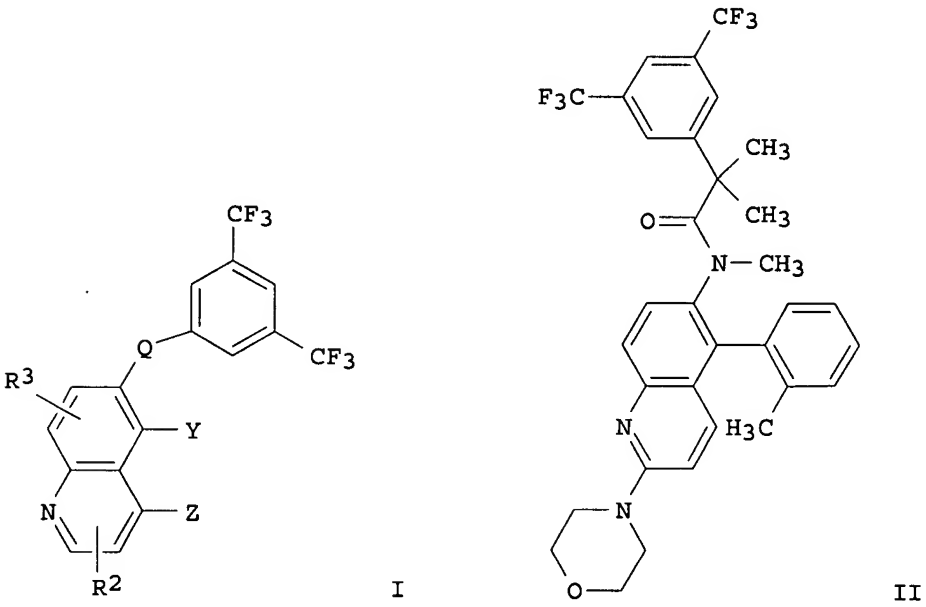


I II

AB Title compds. I [wherein Q = -OCH2-, -OCH(CH3)-, Me-(un)substituted -NHCOCH2-, etc.; one of Y and Z is hydrogen and the other is (un)substituted phenyl; R2, R3 = H, (un)substituted alkyl, oxo, etc.] and N-oxides, pharmaceutically acceptable salts, and individual enantiomers and diastereomers thereof, which are useful as neurokinin-1 (NK-1) receptor antagonists, and inhibitors of tachykinin and in particular substance P (no data), were prepared For instance, amidation of 5-(2-methylphenyl)-2-(morpholin-4-yl)quinolin-6-amine (preparation given) with 2-[3,5-bis(trifluoromethyl)phenyl]-2-methylpropanoic acid mediated by EDC/DMAP in dichloromethane followed by N-methylation with MeI using KHMDS as base gave II. I and their pharmaceutical formulations may be used in the treatment of disorders associated with an excess of tachykinins in a mammal., including emesis, urinary incontinence, depression, and anxiety.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:312133 CAPLUS

DOCUMENT NUMBER: 144:363359

TITLE: Spinal ventral root after-discharges as a pain index: Involvement of NK-1 and NMDA receptors

AUTHOR(S): Yamamoto, Shohei; Honda, Motoko; Tanabe, Mitsuo; Ono, Hideki

CORPORATE SOURCE: Laboratory of CNS Pharmacology, Graduate School of Pharmaceutical Sciences, Nagoya City University, Nagoya, 467-8603, Japan

SOURCE: Brain Research (2006), 1082(1), 115-123
CODEN: BRREAP; ISSN: 0006-8993

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Nociceptive signals are transmitted to the spinal dorsal horn via primary afferent fibers, and the signals induce withdrawal reflexes by activating spinal motoneurons in the ventral horn. Therefore, nociceptive stimuli increase motoneuron firing and ventral root discharges. This study was aimed to develop a method for the study of pain mechanisms and analgesics by recording ventral root discharges. Spinalized rats were laminectomized in the lumbo-sacral region. The fifth lumbar ventral root was sectioned and placed on a pair of wire electrodes. Multi unit efferent discharges from the ventral root were increased by mech. stimulation using a von Frey hair applied to the plantar surface of the hindpaw. The low-intensity mech. stimuli increased the discharges during stimulation (during-discharges) without increasing the discharges after cessation of stimulation (after-discharges), and the high-intensity mech. stimuli increased both during- and after-discharges. Pretreatment with resiniferatoxin, an ultrapotent analog of capsaicin, halved during-discharges and eliminated after-discharges, suggesting that after-discharges are generated by heat- and mechanosensitive polymodal nociceptors. Ezlopitant, a neurokinin-1 (NK-1) receptor antagonist, but not its inactive enantiomer, selectively reduced the after-discharges. Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, preferentially reduced the after-discharges, demonstrating that NK-1 and NMDA receptors mediate the after-discharges. Morphine reduced the after-discharges without affecting during-discharges. By contrast, mephenesin, a centrally acting muscle relaxant, reduced both during- and after-discharges. There results suggest that simultaneous recordings of during- and after-discharges are useful to study pain mechanisms and analgesics as well as to discriminate the analgesic effects from the side effects such as muscle relaxant effects.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:186371 CAPLUS

DOCUMENT NUMBER: 145:201552

TITLE: Emerging drugs for chemotherapy-induced emesis

AUTHOR(S): Navari, Rudolph M.; Province, Paula S.

CORPORATE SOURCE: Notre Dame Cancer Institute, University of Notre Dame, Notre Dame, IN, 46556, USA

SOURCE: Expert Opinion on Emerging Drugs (2006), 11(1), 137-151
CODEN: EOEDA3

PUBLISHER: Ashley Publications Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

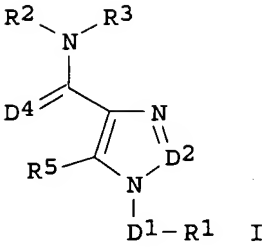
AB A review. Chemotherapy-induced nausea and vomiting (CINV) is associated with a significant deterioration in quality of life. The emetogenicity of the chemotherapeutic agents, repeated chemotherapy cycles and patient risk factors (female gender, younger age, no alc. consumption, history of motion sickness) are the major risk factors for CINV. The use of 5-hydroxytryptamine-3 (5-HT3) receptor antagonists plus dexamethasone has significantly improved the control of acute CINV, but delayed nausea and vomiting remains a significant clin. problem. Two new agents, palonosetron and aprepitant, have recently been approved for the prevention of both acute and delayed CINV. Palonosetron is a 5-HT3 receptor antagonist with a longer half-life and a higher binding affinity than first-generation 5-HT3 receptor antagonists. Aprepitant is the first agent available in the new drug class of neurokinin-1 receptor (NK-1) antagonists. There are a number of 5-HT3 receptor antagonists and NK -1 receptor antagonists currently in Phase II and III clin. trials. Revised antiemetic guidelines for the prevention of CINV are reviewed. Future studies may consider the use of palonosetron

animals. Morphine-induced hyperalgesia was reversed by spinal administration of an NK-1 receptor antagonist in rats and mice, and was observed in wildtype (NK-1+/+), but not NK-1 receptor knockout (NK-1-/-), mice. These data support a critical role for the NK-1 receptor in the expression of sustained morphine-induced hyperalgesia. Addnl., these data indicate that sustained opiate administration induces changes reminiscent of those associated with inflammatory pain. These opiate-induced changes might produce unintended deleterious actions in the course of pain treatment in patients. Understanding of sustained morphine-induced neurochem. changes will help identify approaches that limit the deleterious actions of opiates.

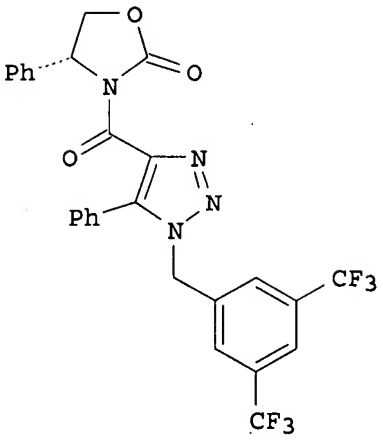
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 11 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:543090 CAPLUS
TITLE: Synthesis of a Merck NK-1 receptor antagonist
AUTHOR(S): Kowal, Jason J.
CORPORATE SOURCE: Process Research, Merck & Co., Rahway, NJ, 07065, USA
SOURCE: Abstracts, 37th Middle Atlantic Regional Meeting of the American Chemical Society, New Brunswick, NJ, United States, May 22-25, 2005 (2005), GENE-699. American Chemical Society: Washington, D. C.
CODEN: 69GVWG
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Substance P (NK-1) receptor antagonists have been shown to be potential therapeutic agents for a wide variety of important medical disorders. Among these, substance P has been shown to be effective in the treatment of chemotherapy-induced nausea and vomiting which led Merck to the identification of Aprepitant. Herein, we describe the synthesis of another Merck NK-1 receptor antagonist.

L7 ANSWER 12 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:526230 CAPLUS
DOCUMENT NUMBER: 143:57917
TITLE: Hippocampal neurokinin-1 receptor and brain-derived neurotrophic factor gene expression is decreased in rat models of pain and stress
AUTHOR(S): Duric, V.; McCarson, K. E.
CORPORATE SOURCE: Department of Pharmacology, Toxicology and Therapeutics, University of Kansas Medical Center, Kansas City, KS, 66160, USA
SOURCE: Neuroscience (Oxford, United Kingdom) (2005), 133(4), 999-1006
CODEN: NRSCDN; ISSN: 0306-4522
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Acute or chronic stress can alter hippocampal structure, cause neuronal damage, and decrease hippocampal levels of the neurotrophin brain-derived neurotrophic factor (BDNF). The tachykinin substance P and its neurokinin-1 (NK-1) receptor may play a critical role in neuronal systems that process nociceptive stimuli; their importance in stress-activated systems has recently been demonstrated by the antidepressant-like actions of NK-1 receptor antagonists.
However, the functional similarities between neurokinin receptors in the hippocampus and those in sensory systems are poorly understood, as is the significance of hippocampal NK-1 receptor in the context of chronic pain. Therefore, the authors investigated the effects of



I



II

AB The present invention relates to selective NK-1 receptor antagonists I [D1 = alkanediyl; D2 = CH, N; D4 = O, S; R1 = (un)substituted Ph; R2 = OH, alkyl, (un)substituted Ph, naphthyl, etc.; R3 = alkyl, phenylalkyl, (un)substituted Ph, COR4, SO2R4; R4 = (un)substituted Ph; or NR2R3 = (un)substituted 4-11 membered heterocyclic ring] or a pharmaceutically acceptable salts thereof, for the treatment of disorders associated with an excess of tachykinins. E.g., a multi-step synthesis of (R)-II, was given. Representative compds. I were tested in the NK-1 receptor binding assay and demonstrated to have binding affinities (Ki values) of ≤100 nM. The pharmaceutical composition comprising the compound I is disclosed.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 16 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:407530 CAPLUS
DOCUMENT NUMBER: 141:289142
TITLE: Localization and functions of neurokinin and N-methyl-D-aspartate receptors
AUTHOR(S): Adam, B.; Liebregts, T.; Gerken, G.; Holtmann, G.
CORPORATE SOURCE: Gastroenterologie/Hepatologie, Universitaetsklinikum Essen, Essen, D-45122, Germany
SOURCE: Falk Symposium (2003), 130(Gastrointestinal Inflammation and Disturbed Gut Function), 253-259
CODEN: FASYDI; ISSN: 0161-5580
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review which discusses the involvement of neurokinin (NK) and N-methyl-D-aspartate (NMDA) receptors in the modulation of visceral hypersensitivity and the possible use of NK-1 receptor antagonists or NMDA receptor antagonists to treat acute or chronic pain.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 17 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:343768 CAPLUS
DOCUMENT NUMBER: 141:405460
TITLE: Risk-benefit of antiemetics in prevention and treatment of chemotherapy-induced nausea and vomiting
AUTHOR(S): Herrstedt, Jorn

CORPORATE SOURCE: Department of Oncology, Copenhagen University Hospital, Herlev, DK-2730, Den.
SOURCE: Expert Opinion on Drug Safety (2004), 3(3), 231-248
CODEN: EODSA9; ISSN: 1474-0338
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The development of effective antiemetic prophylaxis is one of the most significant steps forward in the area of supportive care. Fifteen years ago, patients receiving chemotherapy had to face the fact that nausea and vomiting were inevitable adverse effects, which could only be partially prevented by treatment with antiemetics such as dopamine (DA) D2 receptor antagonists and corticosteroids. The first group of drugs specifically developed as antiemetics was the serotonin (5-hydroxytryptamine [5-HT]3) receptor antagonists. These drugs have dramatically improved prophylaxis of chemotherapy-induced emesis, particularly when used in combination with a corticosteroid. This combination has resulted in a significant decrease in the number of patients vomiting, whereas the improvement in the prophylaxis of nausea has been less successful. Another group of antiemetics, the neurokinin (NK)1 receptor antagonists, has recently been developed, and the first drug in this class, aprepitant, has been approved by the FDA and the EU authorities. Studies have showed that patients benefit from the use of this drug in combination with standard antiemetic therapy (5-HT3 receptor antagonist plus a corticosteroid), both in the acute and delayed phase of nausea and vomiting induced by cisplatin-based chemotherapy. This development has not only led to improved efficacy but also to a decreased risk associated with the use of antiemetics. One of the problems with traditional antiemetics, for example, the DA D2 receptor antagonists, is the risk of unpleasant adverse effects including restlessness and dystonic reactions. To avoid these adverse effects, combination with benzodiazepines or antihistamines was necessary, often resulting in sedation. Modern research also includes pharmacogenomic investigations. This has led to speculation about the importance of drug-drug interactions involving antiemetics through competition for metabolism by the cytochrome P 450 isoenzymes. The worst possible interaction would be a decrease in the effect of different cytotoxins but there is no evidence that such interactions are of importance in daily clin. practice. Guidelines are useful tools in the optimization of antiemetic prophylaxis but, unfortunately, implementation of the evidence-based recommendations is far from successful. A prerequisite for further optimization of antiemetic prophylaxis is updating of the guidelines, including recommendations for the use of NK1 receptor antagonists (aprepitant), followed by implementation of these recommendations in the clinic. Future research must include the difficult trials' focusing on the remaining groups of patients with severe chemotherapy-induced nausea and vomiting, including patients with refractory and breakthrough emesis.

REFERENCE COUNT: 155 THERE ARE 155 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 18 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:240540 CAPLUS
DOCUMENT NUMBER: 141:21656

TITLE: Neurokinin-1 receptor gene expression in the mouse dorsal horn increases with neuropathic pain

AUTHOR(S): Taylor, Bradley K.; McCarson, Kenneth E.
CORPORATE SOURCE: Department of Pharmacology, Tulane University Health Sciences Center, New Orleans, LA, 70118, USA

SOURCE: Journal of Pain (2004), 5(2), 71-76
CODEN: JPOAB5; ISSN: 1526-5900
PUBLISHER: Elsevier Inc.

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Peripheral nerve injury is associated with hyperesthesia and increased neurokinin-1 receptor (NK-1) expression in the dorsal horn of the spinal cord. To test the hypothesis that NK-1 gene expression underlies these responses, we used solution hybridization-nuclease protection assays to quantify NK-1 mRNA levels in dorsal quadrants of the mouse lumbar dorsal horn. Partial sciatic nerve ligation was associated with mech. allodynia, thermal hyperalgesia, and an increase in NK-1 mRNA on the ipsilateral, but not contralateral, side. Regression anal. showed that NK-1 mRNA was significantly correlated with thermal paw withdrawal latency but not mech. threshold. Our results support the idea that substance P is an important mediator of thermal hypersensitivity in the setting of nerve injury and suggest that increased NK-1 receptor transcription precedes increased NK-1 receptor d., ultimately leading to behavioral hypersensitivity to peripheral thermal stimulation. Perspective. The therapeutic efficacy of NK-1 receptor antagonists is unclear. The current data suggest that peripheral nerve injury increases the expression of substance P (NK-1) receptors in the spinal cord dorsal horn; this is correlated with heat hypersensitivity. The analgesic effects of NK-1 antagonists might become apparent if tested against heat-evoked pain in nerve injury patients.
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 19 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:216442 CAPLUS
DOCUMENT NUMBER: 141:21653
TITLE: Nociceptive response to innocuous mechanical stimulation is mediated via myelinated afferents and NK-1 receptor activation in a rat model of neuropathic pain
AUTHOR(S): Pitcher, Graham M.; Henry, James L.
CORPORATE SOURCE: Department of Physiology, McGill University, Montreal, QC, H3G 1Y6, Can.
SOURCE: Experimental Neurology (2004), 186(2), 173-197
CODEN: EXNEAC; ISSN: 0014-4886
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Peripheral nerve injury in humans can produce a persistent pain state characterized by spontaneous pain and painful responses to normally innocuous stimuli (allodynia). Here the authors attempt to identify some of the neurophysiol. and neurochem. mechanisms underlying neuropathic pain using an animal model of peripheral neuropathy induced in male Sprague-Dawley rats by placing a 2-mm polyethylene cuff around the left sciatic nerve according to the method of Mosconi and Kruger. Von Frey hair testing confirmed tactile allodynia in all cuff-implanted rats before electrophysiol. testing. Rats were anesthetized and spinalized for extracellular recording from single spinal wide dynamic range neurons (L3-4). In neuropathic rats (days 11-14 and 42-52 after cuff implantation), ongoing discharge was greater and hind paw receptive field size was expanded compared to control rats. Activation of low-threshold sensory afferents by innocuous mech. stimulation (0.2 N for 3 s) in the hind paw receptive field evoked the typical brief excitation in control rats. However, in neuropathic rats, innocuous stimulation also induced a nociceptive-like afterdischarge that persisted 2-3 min. This afterdischarge was never observed in control rats, and, in this model, is the distinguishing feature of the spinal neural correlate of tactile allodynia. Elec. stimulation of the sciatic nerve at 4 and at 20 Hz each produced an initial discharge that was identical in control and in neuropathic rats. This stimulation also produced an afterdischarge that was similar at the 2 frequencies in control rats. However, in neuropathic

rats, the afterdischarge produced by 20-Hz stimulation was greater than that produced by 4-Hz stimulation. Given that acutely spinalized rats were studied, only peripheral and/or spinal mechanisms can account for the data obtained; as synaptic responses from C fibers begin to fail above approx. 5-Hz stimulation [Pain 46 (1991) 327], the afterdischarge in response to 20-Hz stimulation suggests a change mainly in myelinated afferents and a predominant role of these fibers in eliciting this afterdischarge. These data are consistent with the suggestion that peripheral neuropathy induces phenotypic changes predominantly in myelinated afferents, the sensory neurons that normally respond to mech. stimulation. The NK-1 receptor antagonist, CP-99,994 (0.5 mg/kg, i.v.), depressed the innocuous pressure-evoked afterdischarge but not the brief initial discharge of wide dynamic range neurons, and decreased the elevated ongoing rate of discharge in neuropathic rats. These results support the concept that following peripheral neuropathy, myelinated afferents may now synthesize and release substance P. A result of this is that tonic release of substance P from the central terminals of these phenotypically altered neurons would lead to ongoing excitation of NK-1-expressing nociceptive spinal neurons. In addition, these spinal neurons would also exhibit exaggerated responses to innocuous pressure stimulation. The data in this study put forth a possible neurophysiol. and neurochem. basis of neuropathic pain and identify substance P and the NK-1 receptor as potential neurochem. targets for its management.

REFERENCE COUNT: 204 THERE ARE 204 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 20 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:128806 CAPLUS
DOCUMENT NUMBER: 140:400507
TITLE: Substance P microinjected into the periaqueductal gray matter induces antinociception and is released following morphine administration
AUTHOR(S): Rosen, Annika; Zhang, Yu-Xuan; Lund, Irene; Lundeberg, Thomas; Yu, Long-Chuan
CORPORATE SOURCE: Department of Odontology, Division of Oral and Maxillofacial Surgery, Karolinska Institutet, Huddinge Hospital, Huddinge, SE-141 04, Swed.
SOURCE: Brain Research (2004), 1001(1,2), 87-94
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aims of the present study were to investigate, in rats, the behavioral effects of substance P (SP) microinjected into the ventrolateral periaqueductal gray (PAG) and the effects of the neurokinin 1 (NK -1) receptor antagonist [dArg 1, dTrp 7, 9, Leu 11]-substance P (Spantide). The effect of morphine administration on the release of SP in the ventrolateral PAG was also investigated using microdialysis in awake rats. SP microinjected into the ventrolateral part of the PAG induced significant increases in the hindpaw withdrawal latencies (HWLs) to thermal and mech. stimulation as an antinociceptive response. The NK-1 receptor antagonist blocked these effects but exhibited no antinociceptive effect alone. S.c. administration of morphine increased basal SP-like immunoreactivity (SP-LI) release in the microdialyzate obtained from the ventrolateral PAG of freely moving rats. The authors' results demonstrate that SP injected into the ventrolateral PAG induces an antinociceptive effect via activation of NK-1 receptors. Morphine administered systemically induces the release of SP in the ventrolateral PAG. The authors suggest that an increased release of SP in the PAG may contribute

based on determining specific single nucleotide polymorphisms in the NKNA gene and determining the efficacy and compatibility of a pharmaceutically active compound in the human by reference to polymorphism in NKNA. The invention further relates to isolated nucleic acids comprising within their sequence the polymorphisms as defined herein, to nucleic acid primers and oligonucleotide probes capable of hybridizing to such nucleic acids and to a diagnostic kit comprising one or more of such primers and probes for detecting a polymorphism in the NKNA gene, to a pharmaceutical pack comprising neurokinin-1 (NK-1) receptor antagonists and instructions for administration of the drug to human beings tested for the polymorphisms as well as to a computer readable medium with the stored sequence information for the polymorphisms in the NKNA gene.

L7 ANSWER 23 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:480998 CAPLUS
DOCUMENT NUMBER: 140:87400
TITLE: Functional relevance of antiemetic control experience using the FLIE questionnaire in a randomised study of the NK-1 antagonist aprepitant
AUTHOR(S): Martin, A. R.; Carides, A. D.; Pearson, J. D.; Horgan, K.; Elmer, M.; Schmidt, C.; Cai, B.; Chawla, S. P.; Grunberg, S. M.
CORPORATE SOURCE: Merck Research Labs, Blue Bell, PA, 19422, USA
SOURCE: European Journal of Cancer (2003), 39(10), 1395-1401
CODEN: EJCAEL; ISSN: 0959-8049
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Little information exists on the functional impact of effective antiemetic protection. In the present study, the Functional Living Index-Emesis (FLIE), was used to assess patient-reported impact of chemotherapy-induced nausea and vomiting (CINV) after administration of a new NK-1 receptor antagonist (aprepitant). Cisplatin-treated patients in a double-blind randomized trial received either aprepitant + dexamethasone + ondansetron on day 1 and aprepitant + dexamethasone on days 2-5 or standard antiemetic therapy (dexamethasone and ondansetron on day 1 and dexamethasone on days 2-5). Emetic events, nausea ratings and rescue medications were recorded in a 5-day diary and the FLIE was completed on day 6. Compared with standard therapy, significantly more patients treated with the high dose aprepitant regimen achieved a Complete Response (71 vs. 44%, P<0.001) and also reported no impact on daily life as indicated by the FLIE total score (84 vs. 66%, P<0.01). Use of the FLIE demonstrated that improved control of emesis was highly effective in reducing the impact of CINV on patients' daily lives.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 24 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:428724 CAPLUS
DOCUMENT NUMBER: 140:12261
TITLE: Peripheral tachykinin receptors as potential therapeutic targets in visceral diseases
AUTHOR(S): Lecci, Alessandro; Maggi, Carlo Alberto
CORPORATE SOURCE: Pharmacology Department of Menarini Ricerche, Florence, 50131, Italy
SOURCE: Expert Opinion on Therapeutic Targets (2003), 7(3), 343-362
CODEN: EOTTAO; ISSN: 1472-8222
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. More than 10 yr of intensive preclin. investigation of selective tachykinin (TK) receptor antagonists has provided a rationale to the speculation that peripheral neurokinin (NK)-1, -2 and -3 receptors may be involved in the pathophysiol. of various human diseases at the visceral level. In the airways, despite promising effects in animal models of asthma, pilot clin. trials with selective NK-1 or -2 receptor antagonists in asthmatics have been ambiguous, whereas the potential antitussive effects of NK-1, -2 or -3 antagonists have not yet been verified in humans. In the gastrointestinal (GI) tract, irritable bowel syndrome (IBS) and pancreatitis are appealing targets for peripherally-acting NK-1 and -2 antagonists, resp. In the genitourinary tract, NK-1 receptor antagonists could offer some protection against nephrotoxicity and cytotoxicity induced by chemotherapeutic agents, whereas NK-2 receptor antagonists appear to be promising new agents for the treatment of neurogenic bladder hyperreflexia. Finally, there is preclin. evidence for hypothesizing an effect of NK-3 receptor antagonists on the cardiovascular disturbance that characterizes pre-eclampsia. Other more speculative applications are also mentioned.

REFERENCE COUNT: 224 THERE ARE 224 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 25 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2003:221680 CAPLUS
DOCUMENT NUMBER: 138:238002
TITLE: Preparation of tetrahydropyran derivatives as NK-1 receptor antagonists
INVENTOR(S): Castro Pineiro, Jose Luis; Shaw, Duncan Edward; Williams, Brian John
PATENT ASSIGNEE(S): Merck Sharp & Dohme Limited, UK
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003022839	A1	20030320	WO 2002-GB4085	20020906
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2459464	A1	20030320	CA 2002-2459464	20020906
EP 1427723	A1	20040616	EP 2002-755343	20020906
EP 1427723	B1	20060607		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002012454	A	20041019	BR 2002-12454	20020906
CN 1578778	A	20050209	CN 2002-821470	20020906
JP 2005506329	T	20050303	JP 2003-526914	20020906
AT 328881	T	20060615	AT 2002-755343	20020906
US 2004254184	A1	20041216	US 2004-488842	20040304
IN 2004CN00723	A	20060113	IN 2004-CN723	20040406

L7 ANSWER 28 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:834413 CAPLUS
DOCUMENT NUMBER: 138:331221
TITLE: Gabapentin and the neurokinin1 receptor antagonist Cl-1021 act synergistically in two rat models of neuropathic pain
AUTHOR(S): Field, Mark J.; Gonzalez, M. Isabel; Tallarida, Ronald J.; Singh, Lakhbir
CORPORATE SOURCE: Department of Biology, Pfizer Global Research and Development, Cambridge Laboratories, Cambridge University, Cambridge, UK
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2002), 303(2), 730-735
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The present study examines the effect of combinations of gabapentin (Neurontin) and a selective neurokinin (NK)1 receptor antagonist, 1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[(1-phenylethyl)amino]ethyl]-2-benzofuranylmethyl ester (Cl-1021), in two models of neuropathic pain. Dose responses to both gabapentin and Cl-1021 were performed against static allodynia induced in the streptozocin and chronic constriction injury (CCI) models. Theor. additive lines were calculated from these data. Dose responses to various fixed dose ratios of a gabapentin/Cl-1021 combination were then examined in both models. In the streptozocin model, administration of gabapentin/Cl-1021 combinations at fixed dose ratios of 1 : 1 and 60 : 1 resulted in an additive effect with dose response similar to the theor. additive line. However, a synergistic interaction was seen after fixed dose ratios of 10 : 1, 20 : 1, and 40 : 1 with static allodynia completely blocked and the dose responses shifted approx. 8-, 30-, and 10-fold leftward, resp., from the theor. additive values. In the CCI model, after fixed dose ratios of 5 : 1 and 20 : 1, combinations of gabapentin and Cl-1021 produced an additive response. At the fixed dose ratio of 10:1 static allodynia was completely blocked with an approx. 10-fold leftward shift of the dose response from the theor. additive value, indicating synergy. The combination of gabapentin with a structurally unrelated NK1 receptor antagonist, (2S,3S)-3-(2-methoxybenzylamino)-2-phenylpiperidine (CP-99994), also produced synergy, at a fixed dose ratio of 20 : 1. This ratio completely blocked streptozocin-induced static allodynia and was approx. shifted leftward 5-fold from the theor. additive value. These data suggest a synergistic interaction between gabapentin and NK1 receptor antagonists in animal models of neuropathic pain.
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 29 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:814124 CAPLUS
DOCUMENT NUMBER: 137:337789
TITLE: Preparation of 3-(piperazinylalkyl)-4-quinolinecarboxamide derivatives as NK-3 and NK-2 receptor antagonists for treatment of respiratory diseases and CNS disorders
INVENTOR(S): Farina, Carlo; Gagliardi, Stefania; Giardina, Giuseppe Arnaldo Maria; Martinelli, Marisa
PATENT ASSIGNEE(S): Glaxosmithkline S.P.A., Italy
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 34 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:157756 CAPLUS
DOCUMENT NUMBER: 136:200096
TITLE: Preparation of tetrahydropyran derivatives as nk-1 receptor antagonists
INVENTOR(S): Castro Pineiro, Jose Luis; Owen, Simon Neil; Seward, Eileen Mary; Swain, Christopher John; Williams, Brian John
PATENT ASSIGNEE(S): Merck Sharp & Dohme Limited, UK
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002016344	A1	20020228	WO 2001-GB3699	20010817
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001079950	A5	20020304	AU 2001-79950	20010817
US 2002035132	A1	20020321	US 2001-933064	20010820
US 6489343	B2	20021203		

PRIORITY APPLN. INFO.: GB 2000-20721 A 20000822
WO 2001-GB3699 W 20010817
OTHER SOURCE(S): MARPAT 136:200096
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I (R1 or R2 are independently F or CF3; R3 = Me, CH2OH; R4 = H, OH, alkenyl, alkynyl, N3, substituted amine, etc.; n = 0, 1, or 2); and pharmaceutically acceptable salts thereof are prepared and disclosed as nk-1 receptor antagonists. Thus, II was prepared in five steps from (E)-(R,S)-5-(tetrahydro-2H-pyran-2-yl)oxypent-2-en-1-ol via esterification with 3,4-difluorophenylacetic acid, reduction, dehydration, reduction and etherification of the alc. with (R)-1-(3,5-bis(trifluoromethyl)phenyl)ethanol. As nk-1 receptor antagonists, I are of particular use in the treatment or prevention of depression, anxiety, pain, inflammation, migraine, emesis or postherpetic neuralgia (no data).
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 35 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:157755 CAPLUS
DOCUMENT NUMBER: 136:200095
TITLE: Preparation of difluorophenyltetrahydropyran derivatives as nk-1

receptor antagonists
INVENTOR(S): Castro Pineiro, Jose Luis; Owen, Simon Neil; Seward, Eileen Mary; Swain, Christopher John; Williams, Brian John
PATENT ASSIGNEE(S): Merck Sharp & Dohme Limited, UK
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002016343	A1	20020228	WO 2001-GB3685	20010817
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001078626	A5	20020304	AU 2001-78626	20010817
US 2002035132	A1	20020321	US 2001-933064	20010820
US 6489343	B2	20021203		

PRIORITY APPLN. INFO.: GB 2000-20721 A 20000822
WO 2001-GB3685 W 20010817
OTHER SOURCE(S): MARPAT 136:200095
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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I (R = CHO, alkenyl, (un)substituted piperidine; n = 0 or 1); and pharmaceutically acceptable salts thereof are prepared and disclosed as nk-1 receptor antagonists.
Thus, II was prepared by etherification of 3-(3,4-difluorophenyl)-4-vinyltetrahydropyran-2-ol with (R)-1-(3,5-bis(trifluoromethyl)phenyl)ethanol with successive ozonolysis of the vinyl group, amidation, and reduction As nk-1 receptor antagonists, I are of particular use in the treatment or prevention of depression, anxiety, pain, inflammation, migraine, emesis or postherpetic neuralgia (no data).
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 36 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:122330 CAPLUS
DOCUMENT NUMBER: 137:288839
TITLE: Attenuation of hyperalgesia in a rat model of neuropathic pain after intrathecal pre- or post-treatment with a neurokinin-1 antagonist
AUTHOR(S): Cahill, Catherine M.; Coderre, Terence J.
CORPORATE SOURCE: Pain Mechanisms Laboratory, Clinical Research Institute of Montreal, Montreal, QC, Can.
SOURCE: Pain (2002), 95(3), 277-285
CODEN: PAINDB; ISSN: 0304-3959
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Although many studies have demonstrated a role for substance P in pain, there have been conflicting reports implicating the involvement of substance P in neuropathic pain models. In this study, the non-peptide neurokinin-1 (NK-1) receptor antagonist, L-732,138 was chronically administered by intrathecal (i.t.) injection to rats with mono-neuropathy produced by sciatic nerve constriction. Rats exhibited tactile allodynia and cold hyperalgesia over a 16-day testing period. L-732,138 (5-200 nmol) administered i.t. prior to and for 3 consecutive days post-surgery attenuated the mech. allodynia and cold hyperalgesia on days 4 and 8 post-surgery. The effects of i.t. L-732,138 were also determined in rats with established nerve injury-induced neuropathy. The NK-1 receptor antagonist was injected for 4 consecutive days starting on day 8 post-sciatic nerve injury. Administration of L-732,138 (5-200 nmol) i.t. produced both anti-allodynic and anti-hyperalgesic effects on day 12, but the effect was not permanent, as nociceptive thresholds were similar to controls by day 16. These results demonstrate that substance P is involved both in the induction and the maintenance of neuropathic pain and provides justification for the development and administration of substance P antagonists for the management of clin. neuropathic pain.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 37 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:851115 CAPLUS

DOCUMENT NUMBER: 136:5907

TITLE: Synthesis of aryl-amido-cyclohexane derivatives and their use as NK-1 receptor antagonists

INVENTOR(S): Castro Pineiro, Jose Luis; Dinnell, Kevin; Elliott, Jason Matthew; Hollingworth, Gregory John; Shaw, Duncan Edward; Swain, Christopher John

PATENT ASSIGNEE(S): Merck Sharp & Dohme Limited, UK

SOURCE: PCT Int. Appl., 199 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001087838	A1	20011122	WO 2001-GB2145	20010516
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2408849	A1	20011122	CA 2001-2408849	20010516
EP 1286967	A1	20030305	EP 2001-929829	20010516
EP 1286967	B1	20060927		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003533509	T	20031111	JP 2001-584234	20010516
AT 340781	T	20061015	AT 2001-929829	20010516
US 2003236250	A1	20031225	US 2002-276127	20021113
US 7105507	B2	20060912		

EP 1165540	B1	20030813			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
AU 746251	B2	20020418	AU 2000-33042		20000316
HU 200200441	A2	20020729	HU 2002-441		20000316
JP 2002540107	T	20021126	JP 2000-606588		20000316
AT 247096	T	20030815	AT 2000-911045		20000316
ES 2203434	T3	20040416	ES 2000-911045		20000316
ZA 2001006844	A	20020820	ZA 2001-6844		20010820
IN 2001CN01225	A	20050304	IN 2001-CN1225		20010903
US 6458830	B1	20021001	US 2001-936343		20010910
PRIORITY APPLN. INFO.:			GB 1999-6480	A	19990319
			GB 1999-24616	A	19991018
			WO 2000-GB974	W	20000316

OTHER SOURCE(S): MARPAT 133:266729
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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Substituted tetrahydropyrans I [R1, R4 = H, halo, alkyl, alkoxy, fluoroalkyl, fluoroalkoxy, cycloalkyl(alkyl), NO2, CN, SRa, SORa, SO2Ra, CO2Ra, CONRaRb (Ra or Rb = H, alkyl), alkenyl, alkynyl, alkoxy(alkyl); R2, R5 = H, halo, alkyl, fluoroalkyl, alkoxyalkoxy; R3 = H, halo, fluoroalkyl; R6 = H, alkyl, hydroxyalkyl; R7 = halo, hydroxy, (un)substituted alkenyl, (un)substituted alkynyl, N3, -NR11R12, -NRaCORb, -OSO2Ra, -(CH2)pNRa(CH2)qCOORb (p or q = 1, 2), CORa, COORa, -N=C=O, or N/O/S heterocycle bound at N optionally substituted by oxo, thioxo, halogen, hydroxy, thiol, CORa, CO2Ra, -ZNR11R12 (Z = bond, cyclo(alkylene)), alkyl, hydroxyalkyl, haloalkyl, alkoxy, fluoroalkoxy or alkoxy substituted by a alkoxy or hydroxyl group (R11 = H, alkyl, cycloalkyl, cycloalkylalkyl, alkyl substituted by alkoxy or hydroxyl group, five or six membered N heterocycle; R12 = H, alkyl, cycloalkyl, cycloalkylalkyl, alkyl substituted by alkoxy or hydroxyl group); R8 = hydrogen, alkyl, fluoroalkyl, hydroxy, alkoxy, hydroxyalkyl; R9 or R10 = H, halo, alkyl, oxo, CO2Ra, CONRaRb, CH2ORc (Rc = H, alkyl, phenyl); n = 0, 1 or 2] and pharmaceutically acceptable salts thereof were prepared as neurokinin 1 (NK-1) receptor antagonists. Thus, tetrahydropyran II (R = Me2N) was prepared via nucleophilic substitution of the corresponding mesylate II (R = MeSO2O). The compds. are of particular use in the treatment or prevention of depression, anxiety, pain, inflammation, migraine, emesis or postherpetic neuralgia (no data).

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 43 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:528156 CAPLUS
DOCUMENT NUMBER: 133:359051
TITLE: A new class of antiemetics:The NK-1 receptor antagonists
AUTHOR(S): Bleiberg, Harry
CORPORATE SOURCE: Department of Medicine, Institut Jules Bordet, Brussels, 1000, Belg.
SOURCE: Current Opinion in Oncology (2000), 12(4), 284-288
CODEN: CUOOE8; ISSN: 1040-8746
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Emesis is one of the most unpleasant and debilitating side effects of anticancer chemotherapy. In acute emesis (vomiting occurring 0-24 h after chemotherapy administration), the 5-HT3 receptor antagonists

and corticosteroids are highly effective, with few significant side effects, and can safely be combined. Delayed emesis (vomiting occurring >24 h after chemotherapy administration), however, is both not well understood and less well controlled. Studies have yielded conflicting results concerning the use of 5-HT3 receptor antagonists alone in delayed emesis. The data of NK-1 receptor antagonists in the control of acute emesis, although promising, need confirmation in a properly designed study.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 44 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:412296 CAPLUS
DOCUMENT NUMBER: 133:115233
TITLE: Recent advances in neurokinin-3 receptor antagonists
AUTHOR(S): Giardina, Giuseppe A. M.; Grugni, Mario; Raveglia, Luca F.
CORPORATE SOURCE: Department of Medicinal Chemistry, SmithKline Beecham SpA, Milan, 20021, Italy
SOURCE: Expert Opinion on Therapeutic Patents (2000), 10(6), 939-960
CODEN: EOTPEG; ISSN: 1354-3776
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 117 refs., of recent highlights and progress made in the neurokinin-3 (NK-3) receptor area since 1997. Whereas in the neurokinin-1 (NK-1) and neurokinin-2 (NK-2) biol. areas literature information based on clin. data account for a high therapeutic potential (in emesis and depression for NK-1 and asthma for NK-2 receptor antagonists), there is a total deficiency of information from NK-3 receptor antagonists in clin. development. No other chemical classes in addition to dichlorophenylalkylpiperidines, represented by SR 142,801 and quinolines, represented by SB-222200 and SB-223412, have been identified by pharmaceutical companies and scientists involved in the specific field. Biol. evidence indicates pain/inflammation as a suitable CNS-related therapeutic target, this conclusion is based on localization studies and efficacy of selected NK-3 receptor antagonists in rat disease models of inflammatory pain. In the periphery, the most likely therapeutic indications might be pulmonary and gastrointestinal tract diseases. It is clearly still premature to anticipate any therapeutic potential in man.

REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 45 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:368301 CAPLUS
DOCUMENT NUMBER: 133:4605
TITLE: Preparation of quinoline-4-carboxamide derivatives as NK-3 and NK-2 receptor antagonists
INVENTOR(S): Farina, Carlo; Giardina, Giuseppe; Grugni, Mario; Morvan, Marcel; Nadler, Guy Margueritte Marie Gerard; Raveglia, Luca Francesco
PATENT ASSIGNEE(S): Smithkline Beecham S.P.A., Italy; Smithkline Beecham Laboratoires Pharmaceutiques
SOURCE: PCT Int. Appl., 84 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine is specifically claimed.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 51 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:778223 CAPLUS
DOCUMENT NUMBER: 132:88477
TITLE: Spinal opioid analgesia: how critical is the regulation of substance P signaling?
AUTHOR(S): Trafton, Jodie A.; Abbadie, Catherine; Marchand, Serge; Mantyh, Patrick W.; Basbaum, Allan I.
CORPORATE SOURCE: Departments of Anatomy and Physiology and W. M. Keck Foundation for Integrative Neuroscience, University of California San Francisco, San Francisco, CA, 94143, USA
SOURCE: Journal of Neuroscience (1999), 19(21), 9642-9653
CODEN: JNRSDS; ISSN: 0270-6474
PUBLISHER: Society for Neuroscience
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Although opioids can reduce stimulus-evoked efflux of substance P (SP) from nociceptive primary afferents, the consequences of this reduction on spinal cord nociceptive processing has not been studied. Rather than assaying SP release, in the present study the authors examined the effect of opioids on two postsynaptic measures of SP release, Fos expression and neurokinin-1 (NK-1) receptor internalization, in the rat. The functional significance of the latter was first established in in vitro studies that showed that SP-induced Ca2+ mobilization is highly correlated with the magnitude of SP-induced NK-1 receptor internalization in dorsal horn neurons. Using an in vivo anal., it was found that morphine had little effect on noxious stimulus-evoked internalization of the NK-1 receptor in lamina I neurons. However, internalization was reduced when morphine was co-administered with a dose of an NK-1 receptor antagonist that by itself was without effect. Thus, although opioids may modulate SP release, the residual release is sufficient to exert maximal effects on the target NK-1 receptors. Morphine significantly reduced noxious stimulus-induced Fos expression in lamina I, but the Fos inhibition was less pronounced in neurons that expressed the NK-1 receptor. Taken together, these results suggest that opioid analgesia predominantly involves postsynaptic inhibitory mechanisms and/or presynaptic control of non-SP-containing primary afferent nociceptors.
REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 52 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:775080 CAPLUS
DOCUMENT NUMBER: 132:235211
TITLE: The role of the spinal opioid receptor like 1 receptor, the NK-1 receptor, and cyclooxygenase-2 in maintaining postoperative pain in the rat
AUTHOR(S): Yamamoto, Tatsuo; Sakashita, Yoshihiko
CORPORATE SOURCE: Department of Anesthesiology, Chiba University School of Medicine, Chiba, 260, Japan
SOURCE: Anesthesia & Analgesia (Baltimore) (1999), 89(5), 1203-1208
CODEN: AACRAT; ISSN: 0003-2999
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Postoperative incident pain is not easily treated with opioids. Mech. hyperalgesia induced by skin incision in rats is one of the animal models of postoperative incident pain. It is thought that mech.

hyperalgesia is maintained by the sensitization of spinal dorsal horn neurons. The NK-1 receptor, the opioid receptor like 1 (ORL1) receptor, and cyclooxygenase (COX)-2 reportedly are involved in the development of spinal sensitization. In this study, the authors clarified the role of the NK-1 receptor, the ORL1 receptor, and COX-2 in the maintenance of mech. hyperalgesia induced by skin incision. A 1-cm longitudinal incision was made through skin and fascia of the plantar aspect of the right foot in the rat. Four hours after the skin incision, significant mech. hyperalgesia developed. An ORL1 receptor agonist (nociceptin), NK -1 receptor antagonists (CP-96,345 and FK888), and COX-2 inhibitors (NS398 and JTE522) were administered intrathecally 4 h after the skin incision. An ORL1 receptor agonist and NK-1 receptor antagonists, but not COX-2 inhibitors, significantly attenuated the level of mech. hyperalgesia induced by the skin incision. These findings suggest that the spinal ORL1 receptor and the NK-1 receptor play an important role in maintaining the mech. hyperalgesia induced by skin incision. Implications: Intrathecal injection of an NK-1 receptor antagonist and an ORL1 receptor agonist may be effective for the treatment of postoperative incident pain.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 53 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:645915 CAPLUS
DOCUMENT NUMBER: 132:30896
TITLE: Tachykinins and in vivo gut motility
AUTHOR(S): Sarna, Sushil K.
CORPORATE SOURCE: Departments of Surgery and Physiology, Medical College of Wisconsin and Zablocki VA Medical Center, Milwaukee, WI, 53226, USA
SOURCE: Digestive Diseases and Sciences (1999), 44(8, Suppl.), 114S-118S
CODEN: DDSCDJ; ISSN: 0163-2116
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 28 refs. The gut smooth muscle in the intact conscious state exhibits three distinct types of contractions: rhythmic phasic contractions, tone, and ultrapropulsive contractions. The motility functions of these contractions differ markedly. The phasic contractions mix and propel the ingested food in an orderly fashion so that the nutrients can be absorbed. The ultrapropulsive contractions are of two types, giant migrating contractions (GMCs) and retrograde giant contractions (RGCs). GMCs produce mass movements in the caudal direction and RGCs in the oral direction. GMCs are associated with the symptoms of diarrhea, abdominal cramping, tenesmus, and urgency of defecation. The RGCs regurgitate the contents of the upper small intestine into the stomach in preparation of their expulsion by the somatomotor response. Tachykinins and their receptors are strategically located on the enteric, neurons and smooth muscle cells to regulate the above contractions. Recent findings show that NK-1 receptors located on colonic circular smooth muscle cells may mediate colonic GMCs, whereas NK-3 receptors located on presynaptic neurons may mediate the small intestinal GMCs. The mol. and cellular mechanisms of stimulation of RGCs are not known. NK-1 receptor antagonists have shown potential therapeutic effects on vomiting induced by a variety of stimuli in exptl. animals.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 54 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:558391 CAPLUS

CORPORATE SOURCE: Center for Studies in Behavioral Neurobiology, Department of Psychology, Concordia University, Montreal, QC, H3G 1M8, Can.
SOURCE: Physiology & Behavior (1999), 66(4), 717-721
CODEN: PHBHA4; ISSN: 0031-9384
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Substance P (SP) receptors in the ventral tegmental area (VTA) play a critical role in mediating the stress-induced activation of midbrain ascending dopamine neurons. Interestingly, SP acting in the VTA induces analgesia in the formalin test for tonic pain. Because exposure to stress inhibits pain in this test, we speculated that SP receptors in the VTA might mediate stress-induced analgesia. The present study explored this idea by examining the effect of blocking tachykinin NK-1 receptors in the VTA on foot-shock stress-induced analgesia in the formalin test. Intra-VTA infusions of the novel tachykinin NK-1 receptor antagonist, RP-67580, prevented this response. This finding suggests that exposure to stress inhibits tonic pain through the release of endogenous SP in the VTA.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 59 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:780857 CAPLUS
DOCUMENT NUMBER: 130:148575
TITLE: Effect of tachykinin receptor antagonists in experimental neuropathic pain
AUTHOR(S): Coudore-Civiale, Marie-Ange; Courteix, Christine; Eschalier, Alain; Fialip, Joseph
CORPORATE SOURCE: BP 38, Faculte de Pharmacie, Laboratoire de Pharmacologie, Equipe NPPUA (NeuroPsychoPharmacologie, Universite d'Auvergne), Clermont-Ferrand, 63001, Fr.
SOURCE: European Journal of Pharmacology (1998), 361(2/3), 175-184
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The intrathecal effect of 0.1 to 10 μg of RP-67,580 (3aR,7aR)-7,7-diphenyl-2[1-imino-2(2-methoxyphenyl)-ethyl]perhydroisoindol-4-onehydro chloride, CP-96,345 (2S,3S)-cis-(2(diphenylmethyl)-N-[(2-methoxyphenyl) methyl]-1-azabicyclo[2.2.2]octan-3-amine), SR- 140,333 (S)-(1-{2-[3-(3,4-dichlorophenyl)-1-(3-isopropoxyphenylacetyl)piperidin-3-yl]ethyl}-4-phenyl-1-azonia-bicyclo[2.2.2]- Octane,chloride), all neurokinin (NK)1-receptor antagonists, SR-48,968 (S)-N-methyl-N[4-(4-acetylamino-4-[phenylpipe- ridino)-2-(3,4-dichlorophenyl)-butyl]benzamide, a tachykinin NK2 receptor antagonist and SR-142,801 (S)-(N)-(1-(3-(1-benzoyl-3-(3,4-dichlorophenyl) piperidin-3-yl)propyl)-4-phenylpiperidin-4-yl)-N-Me acetamide, a tachykinin NK3 receptor antagonist, and of their resp. inactive enantiomers on thresholds of vocalization due to a mech. stimulus in mononeuropathic (sciatic nerve ligature) and diabetic rats, was examined The tachykinin NK1 and the NK2 receptor antagonists were antinociceptive in both models, with a higher effect of the former in diabetic rats. The tachykinin NK3 receptor antagonist was weakly effective in diabetic rats only. This indicates a differential involvement of the tachykinins according to the model of neuropathic pain, suggesting a potential role for tachykinin receptor antagonists in the treatment of neuropathic pain.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 60 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:724213 CAPLUS
DOCUMENT NUMBER: 130:38715
TITLE: Preparation of substituted benzamides and their use for treatment of respiratory disorders, headache, and emesis
INVENTOR(S): Sakurada, Tsukasa; Sasaki, Jun; Oba, Masataka; Matsumura, Yasushi
PATENT ASSIGNEE(S): Asahi Glass Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 11 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 10298197	A	19981110	JP 1997-109581	19970425

PRIORITY APPLN. INFO.: JP 1997-109581 19970425
OTHER SOURCE(S): MARPAT 130:38715
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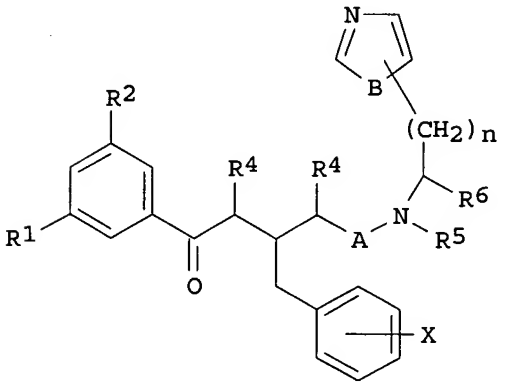

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AB Substituted benzamides I [A = CO, CH2; B = NR3, O, S, CH2; R1, R2 = H, OH, halo, lower (halo)alkyl, etc.; R4, R5 = H, halo, lower alkyl, alkoxy; R6 = H, halo, alkyl, CONR7R8, CO2R9, COR10; X = H, halo, lower (halo)alkyl, alkoxy; n = 0-3; R3 = H, halo, lower alkyl, alkoxy; R7-R10 = H, lower alkyl, aralkyl, aryl; except a case where A = CO, B = NH, R1 = R2 = CF3, R4 = R5 = X = H, R6 = CONH2, and n = 1] or their salts are prepared The benzamides are antagonists of the substance P/NK-1 receptor interaction (no data). Crude N-tert-butoxycarbonylphenylalanylhistamine (3 g) was deprotected by F3CCO2H and treated with 3,5-bis(trifluoromethyl)benzoic acid, HBTU, and HOBT in DMF to give 130 mg N-3,5-bis(trifluoromethyl)benzoylphenylalanylhistamine.

L7 ANSWER 61 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:716122 CAPLUS
DOCUMENT NUMBER: 129:335788
TITLE: Use of NK-1 receptor antagonists for the manufacture of a medicament in the treatment of symptoms of irritable bowel syndrome
INVENTOR(S): Williams, Stephen Alaric

10/566,252

PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 873753	A1	19981028	EP 1998-302747	19980408
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NZ 329807	A	20000728	NZ 1998-329807	19980219
JP 10316567	A	19981202	JP 1998-106398	19980416
CA 2235438	A1	19981023	CA 1998-2235438	19980421
ZA 9803325	A	19991021	ZA 1998-3325	19980421
AU 9863530	A	19981029	AU 1998-63530	19980422
HU 9800938	A2	19990128	HU 1998-938	19980422

PRIORITY APPLN. INFO.: US 1997-44250P P 19970423
OTHER SOURCE(S): MARPAT 129:335788
AB The invention relates to the use of a NK-1 receptor antagonist, in particular a substance P receptor antagonist, for the manufacture of a medicament for the treatment of symptoms of irritable bowel syndrome. An example of such antagonist is (2S,3S)-2-diphenylmethyl-3-(5-tert-butyl-2-methoxybenzyl)amino-1-azabicyclo[2.2.2]octane.
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 62 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:661006 CAPLUS
DOCUMENT NUMBER: 130:60945
TITLE: Antiemetic effects of a novel NK-1 receptor antagonist, HSP-117, in ferrets
AUTHOR(S): Saito, Ryo; Suehiro, Yumiko; Ariumi, Hideto; Migita, Keisuke; Hori, Nobuaki; Hashiguchi, Terusi; Sakai, Michinori; Saeki, Masakazu; Takano, Yukio; Kamiya, Hiro-o
CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, Department of Pharmacology, Fukuoka University, Fukuoka, 814-0180, Japan
SOURCE: Neuroscience Letters (1998), 254(3), 169-172
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A nonpeptide compound, HSP-117, is an antagonist of the tachykinin NK-1 receptor. Binding of [3H]substance P (SP) to the membranes of IM-9 cells was inhibited by the antagonists HSP-117 and CP-99,994, the inhibitory activity of HSP-117 being about 50-fold that of CP-99,994. The SP-induced firing responses of single neuron activity in slices of the nucleus tractus solitarius of ferrets were inhibited by 10 μM HSP-117. Intracerebroventricular injection of HSP-117 inhibited the retching and vomiting induced by copper sulfate and morphine, and the inhibitory effect of HSP-117 on emesis was greater than that of CP-99,994. These results indicate that: (1) HSP-117 is a potent antiemetic agent, blocking NK-1 receptors in the nucleus tractus solitarius; (2) NK-1 receptors in the nucleus tractus solitarius play an important role in emesis induced by broad-spectrum emetic stimuli.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 63 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:632408 CAPLUS
DOCUMENT NUMBER: 130:20189
TITLE: Structural Optimization Affording 2-(R)-(1-(R)-3,5-Bis(trifluoromethyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4- (3-oxo-1,2,4-triazol-5-yl)methylmorpholine, a Potent, Orally Active, Long-Acting Morpholine Acetal Human NK-1 Receptor Antagonist
AUTHOR(S): Hale, Jeffrey J.; Mills, Sander G.; MacCoss, Malcolm; Finke, Paul E.; Cascieri, Margaret A.; Sadowski, Sharon; Ber, Elzbieta; Chicchi, Gary G.; Kurtz, Marc; Metzger, Joseph; Eiermann, George; Tsou, Nancy N.; Tattersall, F. David; Rupniak, Nadia M. J.; Williams, Angela R.; Rycroft, Wayne; Hargreaves, Richard; MacIntyre, D. Euan
CORPORATE SOURCE: Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Journal of Medicinal Chemistry (1998), 41(23), 4607-4614
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Structural modifications requiring novel synthetic chemical were made to the morpholine acetal human neurokinin-1 (hNK-1) receptor antagonist L-742694, and this resulted in the discovery of 2-(R)-(1-(R)-3,5-bis(trifluoromethyl)phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-oxo-1,2,4-triazol-5-yl)methyl morpholine (I). This modified compound is a potent, long-acting hNK-1 receptor antagonist as evidenced by its ability to displace [125I]Substance P from hNK-1 receptors stably expressed in CHO cells (IC50 = 0.09 ± 0.06 nM) and by the measurement of the rates of association (k1 = 2.8 ± 1.1 + 108 M-1 min-1) and dissociation (k-1 = 0.0054 ± 0.003 min-1) of I from hNK-1 expressed in Sf9 membranes which yields Kd = 19 ± 12 pM and a t1/2 for receptor occupancy equal to 154 ± 75 min. Inflammation in the guinea pig induced by a resiniferatoxin challenge (with NK-1 receptor activation mediating the subsequent increase in vascular permeability) is inhibited in a dose-dependent manner by the oral preadmininstration of I (IC50 (1 h) = 0.008 mg/kg; IC90 (24 h) = 1.8 mg/kg), indicating that this compound has good oral bioavailability and peripheral duration of action. Central hNK-1 receptor stimulation is also inhibited by the systemic preadministration of I as shown by its ability to block an NK-1 agonist-induced foot tapping response in gerbils (IC50 (4 h) = 0.04 ± 0.006 mg/kg; IC50 (24 h) = 0.33 ± 0.017 mg/kg) and by its antiemetic actions in the ferret against cisplatin challenge. The activity of I at extended time points in these preclin. animal models sets it apart from earlier morpholine antagonists (such as L-742694), and the piperidine antagonists CP 122721 and GR 205171 and could prove to be an advantage in the treatment of chronic disorders related to the actions of Substance P. In part on the basis of these data, I has been identified as a potential clin. candidate for the treatment of peripheral pain, migraine, chemotherapy-induced emesis, and various psychiatric disorders.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 64 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:529539 CAPLUS
TITLE: The synthesis and evaluation of 2, 3, 5- and 2, 3, 6-trisubstituted morpholine acetal human NK-1 receptor antagonists.
AUTHOR(S): Budhu, R. J.; Hale, J. J.; Mills, S. G.; MacCoss, M.; Cascieri, M. A.; Sadowski, S.; Ber, E.; Metzger, J.;

TITLE: Tachykinins: central and peripheral effects
AUTHOR(S): Birch, P. J.
CORPORATE SOURCE: Germany
SOURCE: Handbook of Experimental Pharmacology (1997), 130(Pharmacology of Pain), 117-133
CODEN: HEPHD2; ISSN: 0171-2004
PUBLISHER: Springer
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with .apprx.105 refs. The tachykinin substance P plays a major role in sensory transmission at both central and peripheral sites. Current evidence suggests that blockade of the action of SP at the NK-1 receptor may provide novel therapeutic treatments for acute pain, chronic pain, migraine headache and emesis. Currently a number of potent, selective non-peptide NK-1 receptor antagonists are undergoing clin. evaluation and clin. data is eagerly awaited.
REFERENCE COUNT: 108 THERE ARE 108 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 70 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:239488 CAPLUS
DOCUMENT NUMBER: 126:312128
TITLE: The non-peptide NK-1 receptor antagonist LY303870 inhibits neurogenic dural inflammation in guinea pigs
AUTHOR(S): Phebus, Lee A.; Johnson, Kirk W.; Stengel, Peter W.; Lobb, Karen L.; Nixon, James A.; Hipskind, Philip A.
CORPORATE SOURCE: Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN, 46285, USA
SOURCE: Life Sciences (1997), 60(18), 1553-1561
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB LY303870 is a competitive, high affinity NK-1 receptor antagonist. It was tested in the trigeminal stimulation-induced neurogenic dural inflammation model of migraine. The neurogenic inflammation theory of migraine pain proposes that substance P, acting through NK-1 receptors, causes dural inflammation which enhances migraine pain. LY303870 administration potently inhibited neurogenic dural inflammation as measured by plasma protein extravasation caused by elec. stimulation of the trigeminal ganglion in guinea pigs. It was active in this model when administered via i.v., oral or inhalation routes. LY306155, the enantiomer of LY303870 with lower affinity for the NK-1 receptor, was much less potent than LY303870 in this model. LY303870, at oral doses of 1, 10 and 100 μg/kg, produced a long, dose-dependent inhibition of dural inflammation, demonstrating a suitable duration of action for a potential use in acute migraine and migraine prophylaxis.

L7 ANSWER 71 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:209401 CAPLUS
DOCUMENT NUMBER: 126:259226
TITLE: Roles of substance P in spinal nociceptive pathways
AUTHOR(S): Henry, J. L.
CORPORATE SOURCE: Departments of Physiology and Psychiatry, McGill University, Montreal, QC, Can.
SOURCE: Neuropeptides, Nociception, and Pain, Symposium, Mainz, Oct. 8-10, 1992 (1994), Meeting Date 1992, 209-220. Editor(s): Hoekfelt, Tomas; Schaible, Hans-Georg; Schmidt, Robert F. Chapman & Hall:

London, UK.
CODEN: 64DPAS
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review, with .apprx.48 refs. Topics discussed include: evidence implicating substance P in mediation of sensory inputs, electrophysiol. studies on effects of NK-1 receptor antagonists on substance P-induced excitation of dorsal horn neurons and on excitation of dorsal horn neurons by noxious cutaneous stimuli, and correlation of electrophysiol. results with immunocytochem.

L7 ANSWER 72 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:654383 CAPLUS
DOCUMENT NUMBER: 125:318357
TITLE: The spinal contribution of substance P to the generation and maintenance of inflammatory hyperalgesia in the rat
AUTHOR(S): Traub, Richard J.
CORPORATE SOURCE: College Medicine, University Iowa, Iowa, IA, USA
SOURCE: Pain (1996), 67(1), 151-161
CODEN: PAINDB; ISSN: 0304-3959
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB That substance P (SP) contributes in some way to spinal nociceptive processing has been known for many years. However, the contribution of SP and NK-1 receptors to the generation and maintenance of inflammatory hyperalgesia or persistent chemical hyperalgesia is not clear. The purpose of this study was to test the hypothesis that SP contributes to the generation but not maintenance of hyperalgesia using two models of inflammatory pain: carrageenan, which allows for testing of acute noxious thermal and mech. stimuli, and formalin, a model of spontaneous pain. Intrathecal pretreatment with the NK -1 receptor antagonist CP-96,345 (100, 50, 25 nmol) dose-dependently attenuated the thermal (46%, 27% and 16%, resp.) and mech. (66%, 37% and 3%, resp.) hyperalgesia produced by 2 mg carrageenan, but not 6 mg carrageenan, 3 h after the induction of inflammation. The attenuation was still apparent at 5 h for the greatest dose, but at 7 h the magnitude of hyperalgesia was equal to rats pretreated with saline. Posttreatment with 100 nmol CP-96,345 following the establishment of hyperalgesia had no effect. Intrathecal pretreatment with 125 nmol CP-96,345 prior to formalin (1% or 5%) injection into the hindpaw produced an overall 29% or 23% attenuation, resp., of the nociceptive behavior during the 1-h observation period. For both 1% and 5% formalin injections, the phase 2 response, but not the phase I response, was significantly lower than that from rats pretreated with saline. Pretreatment with 100 or 125 nmol of the inactive enantiomer, CP-96,344, was no different than pretreatment with saline. A dose of 250 nmol CP-96,345 produced voluntary paralysis yet the flexion reflex to noxious pinch remained. These results support the hypothesis that SP contributes to the generation of inflammatory hyperalgesia but once established, the contribution of SP to maintaining the state of hyperalgesia is reduced. The interaction of SP, NK-1 receptors and spinal NMDA receptors in relation to inflammatory pain is discussed.

L7 ANSWER 73 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:41930 CAPLUS
DOCUMENT NUMBER: 124:77369
TITLE: Electrocorticographic desynchronization after application of visceral and somatic noxious stimuli in urethane-anesthetized rats: effect of intrathecal administration of tachykinin (NK 1 or NK 2) receptor antagonists

dorsal horn neurons in vivo by the NK-1 receptor antagonists CP-96,345 and CP-99,994, but not by CP-96,344

AUTHOR(S): Radhakrishnan, V.; Henry, J. L.
CORPORATE SOURCE: Dep. Physiol. Psychiatry, McGill Univ., Montreal, QC, H3G 1Y6, Can.

SOURCE: Neuroscience (Oxford) (1995), 64(4), 943-58
CODEN: NRSCDN; ISSN: 0306-4522
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Extracellular and intracellular studies were undertaken to test the effects of the non-peptide, substance P (NK-1) receptor antagonists CP-96,345 and CP-99,994, and of CP-96,344, the inactive enantiomer of CP-96,345, on the responses of spinal dorsal horn neurons to peripheral noxious and non-noxious cutaneous stimuli in spinalized cats anesthetized with α-chloralose. The effect of these agents on the response of dorsal horn neurons to iontophoretic application of substance P was also tested in extracellular studies. The substance P-induced slow, prolonged discharge of dorsal horn neurons was blocked by administration (0.5 mg/kg, i.v.) of CP-96,345 or CP-99,994, but was unaffected by CP-96,344. The response of substance P-sensitive neurons to noxious thermal stimulation of the cutaneous receptive field, especially the late afterdischarge phase, was also significantly inhibited by CP-96,345 and by CP-99,994. The response of such neurons to noxious pinch stimulation of the receptive field was also significantly inhibited by CP-96,345 and CP-99,994, but the response of three other substance P-sensitive neurons to pinch was unaffected by CP-96,345. CP-96,344 did not affect the response of any neuron tested to either of these noxious stimuli (noxious thermal,; pinch). The response to hair afferent stimulation was unaffected by any of these compds. (CP-96,345,; CP-96,344,; CP-99,994). In intracellular studies, the effect of these antagonists was tested on responses of dorsal horn neurons to noxious pinch stimulation or to a train of high intensity elec. stimulation of the superficial peroneal nerve. Both stimuli produced an initial fast depolarization followed by a slow and prolonged depolarization with corresponding discharge patterns. CP-96,345 and CP-99,994 selectively blocked the late, slow components of the stimulus-evoked response without affecting the early components. Responses to single elec. pulses of the same intensity and duration were not affected. CP-96,344 did not affect any of the responses tested. The data indicate that nociceptive responses of a subset of spinal dorsal horn cells are selectively blocked by the NK-1 receptor antagonists, CP-96,345 and CP-99,994, thus confirming the involvement of NK-1 receptors in these responses. As CP-96,344 did not affect any of the responses, it is likely that some of the properties common to CP-96,345 and CP-96,344, such as blockade of calcium channels, may not play a significant role in the selective antagonism of nociceptive responses by these non-peptide antagonists.

L7 ANSWER 77 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1993:617216 CAPLUS
DOCUMENT NUMBER: 119:217216

TITLE: CP-99,994, a nonpeptide antagonist of the tachykinin NK1 receptor

AUTHOR(S): McLean, S.; Snider, R. M.; Desai, M. C.; Rosen, T.; Bryce, D. K.; Longo, K. P.; Schmidt, A. W.; Heym, J.
CORPORATE SOURCE: Cent. Res. Div., Pfizer, Inc., Groton, CT, 06340, USA

SOURCE: Regulatory Peptides (1993), 46(1-2), 329-31
CODEN: REPPDY; ISSN: 0167-0115
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This report describes a new nonpeptide NK1 receptor antagonist, CP-99,994

(+)-(2S,3S)-3-(2-methoxybenzylamino)-2-phenylpiperidine. This compound exhibits reduced affinity for the verapamil sensitive Ca2+ channel relative to the quinuclidine NK1 receptor antagonist CP-96,345 and greater affinity for the human NK1 receptor than the perhydroisoindole RP 67580. The implication of substance P in a variety of clin. disorders, including inflammation, chronic pain, asthma, and psychopathol., suggests the possibility of important therapeutic uses for an NK1 receptor antagonist such as CP-99,994.

L7 ANSWER 78 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1993:530745 CAPLUS
DOCUMENT NUMBER: 119:130745
TITLE: Substance P and inflammatory pain: Potential of substance P antagonists as analgesics
AUTHOR(S): Henry, James L.
CORPORATE SOURCE: Dep. Physiol., McGill Univ., Montreal, QC, H3G 1Y6, Can.
SOURCE: Agents and Actions Supplements (1993), 41(Inflammatory Disease Therapy), 75-87
CODEN: AASUDJ; ISSN: 0379-0363
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 66 refs. Substance P has been implicated in peripheral inflammatory responses and recent evidence from animal models indicates that substance P (NK-1 receptor) antagonists are effective in blocking peripheral inflammatory responses as well as nociception (pain) associated with inflammation. Evidence implicating substance P in nociception is reviewed in this survey, along with evidence on the effects of NK-1 receptor antagonists and with some comments on the usefulness of such antagonists as analgesics.

L7 ANSWER 79 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1993:248204 CAPLUS
DOCUMENT NUMBER: 118:248204
TITLE: CP-96,345, but not its stereoisomer, CP-96,344, blocks the nociceptive responses to intrathecally administered substance P and to noxious thermal and chemical stimuli in the rat
AUTHOR(S): Yashpal, K.; Radhakrishnan, V.; Coderre, T. J.; Henry, J. L.
CORPORATE SOURCE: Dep. Psychiatry, McGill Univ., Montreal, QC, H3G 1Y6, Can.
SOURCE: Neuroscience (Oxford, United Kingdom) (1993), 52(4), 1039-47
CODEN: NRSCDN; ISSN: 0306-4522
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of s.c. administration of the nonpeptide NK-1 (substance P) receptor antagonist, CP 96345, and its stereoisomer, CP 96344, were tested in 3 nociceptive paradigms in the rat. In the 1st paradigm, tail-flick responses were monitored before and after intrathecal administration of substance P (6.5 nmol) in rats pretreated s.c. with saline, CP 96344 (5 mg/kg), or CP 96345 (5 mg/kg). In the control groups, pretreated s.c. with saline, CP 96344 (5 mg/kg) or CP 96345 (5 mg/kg). In the control groups, pretreated with saline or with CP 96344, substance P reduced the tail-flick reaction time at 1 min after administration to 38.3 and 32.1% of the mean baseline value, resp. In contrast, in the group pretreated with CP 96345, the reaction time following administration of substance P was 98.8% of the baseline reaction time; this value was not significantly different from the baseline value of this group. In the 2nd paradigm, rats were anesthetized with a mixture of chloral hydrate (120 mg/kg, i.p.) and sodium pentobarbital (20 mg/kg, i.p.), and the effects were determined on

AUTHOR(S): Radhakrishnan, V.; Henry, J. L.
CORPORATE SOURCE: Dep. Physiol., McGill Univ., Montreal, QC, H3G 1Y6, Can.
SOURCE: Neuroscience Letters (1991), 132(1), 39-43
CODEN: NELED5; ISSN: 0304-3940
DOCUMENT TYPE: Journal
LANGUAGE: English
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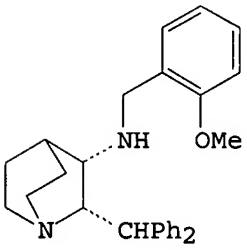

I

AB Responses of dorsal horn neurons to iontophoretic application of substance P (80-120 nA) and to noxious thermal and noxious mech. stimulations of the receptive field in the hind limb were tested in adult cats before and after the administration of the specific, nonpeptide, NK-1 receptor antagonist CP-96,345 (I) (0.5 mg/kg, i.v.). I inhibited the response of the neurons to substance P and also the response of these substance P-sensitive neurons to noxious thermal stimulation. The response of the substance P-insensitive neurons to noxious heat stimulations were, however, unaffected by I. The effect of I on the response of neurons to noxious mech. stimulation was variable. The results confirm the role of substance P in thermal nociception.

L7 ANSWER 82 OF 82 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1992:76952 CAPLUS
DOCUMENT NUMBER: 116:76952
TITLE: Substance P-mediated slow excitatory postsynaptic potential elicited in dorsal horn neurons in vivo by noxious stimulation
AUTHOR(S): De Koninck, Yves; Henry, James L.
CORPORATE SOURCE: Dep. Physiol., McGill Univ., Montreal, QC, H3G 1Y6, Can.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1991), 88(24), 11344-8
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Evidence is presented that CP-96,345, a specific substance P (NK-1) receptor antagonist, selectively blocks a slow, prolonged excitatory postsynaptic potential following noxious cutaneous stimulation or a train of intense elec. stimuli to cat sensory nerves but does not affect the response to innocuous input or the brief response to single elec. stimuli to C fibers. The results indicate the specific involvement of substance P in the mediation of a prolonged after-excitation to noxious stimulation. This may have important implications for the etiol. and treatment of chronic pain and for plastic changes in nociceptive pathways.

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(FILE 'HOME' ENTERED AT 13:11:27 ON 08 MAR 2007)

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     FILE 'CAPLUS' ENTERED AT 13:11:49 ON 08 MAR 2007
L1           294 S NK-1 RECEPTOR ANTAGONIST?
L2            83 S NK-2 RECEPTOR ANTAGONIST?
L3           357 S L1 OR L2
L4         16567 S ANXIETY
L5            37 S L3 AND L4
L6         66031 S IRRITABLE BOWEL SYNDROME OR PAIN OR HEADACHE OR VOMITING
L7            82 S L3 AND L6

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